AMENDMENTS TO THE SPECIFICATION

Please replace paragraph [0008] with the following amended paragraph that corrects a publishing error by the PTO:

[0008] The invention provides recombinant compositions and rapid and efficient methods for generating mini-adenovirus (mAd) vectors which are capable of introducing any nucleotide sequence of interest into a cell, including, but not limited to, in the applications of gene therapy. The invention provides recombinant vectors including adenovirus/~~adeno-associa-ted~~ adeno-associated virus (Ad/AAV) vectors and mAd vectors, as well as cells containing these vectors. The unique configuration of the invention's parental Ad/AAV hybrid vectors overcomes the inefficiency of the prior's methods of generating mAd vectors. Furthermore, the methods of the invention provide an improvement to the methods of generating mAd vectors which are capable of stably packaging and transducing nucleotide sequences of interest.

Please replace paragraph [0009] with the following amended paragraph:

[0009] In one embodiment, the invention provides a recombinant vector, comprising in operable combination: a) a nucleotide sequence of interest having a 5' end and a 3' end; b) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; c) adenovirus packaging sequence linked to one of the inverted terminal repeats; and d) a first adeno-associated virus terminal repeat sequence operably linked to the 3' end of the nucleotide sequence of interest, wherein the vector lacks a second adeno-associated virus terminal repeat sequence. In a preferred embodiment, the vector further comprises an adeno-associated virus terminal repeat D sequence operably linked to the adeno-associated virus terminal repeat sequence to form adeno-associated virus terminal ~~repeat-DD~~ repeat-DD sequence. In another preferred embodiment, the vector further comprises an adeno-associated virus terminal repeat D sequence operably linked to the 5' end of the nucleotide sequence of interest. In yet another preferred embodiment, the packaging sequence is linked to the 5' end or the 3' end of the nucleotide sequence of interest. In yet another preferred embodiment, the

nucleotide sequence of interest comprises adeno-associated virus rep gene region. While not limiting the invention to a particular type of nucleotide sequence, in another preferred embodiment, the nucleotide sequence of interest comprises a reporter gene. Without intending to limit the invention to a particular reporter gene, in a more preferred embodiment, the reporter gene is selected from green fluorescent protein gene, E. coli .beta.-galactosidase gene, human placental alkaline phosphatase gene, and chloramphenicol acetyltransferase gene. In an alternative preferred embodiment, the vector lacks one or more adenovirus genes. In a more preferred embodiment, the vector is a gutted adenovirus vector. In another alternative preferred embodiment, the vector lacks one or more adenovirus early gene region selected from E1, E2, E3, and E4 gene ~~region~~ regions. In a more preferred embodiment, the vector lacks the E1 gene region. In yet a more preferred embodiment, the vector lacks the E1 gene region and further lacks the E3 gene region. In an alternative preferred embodiment, the vector lacks the E3 gene region. In another alternative preferred embodiment, the vector lacks the E4 gene region. In an alternative preferred embodiment, the vector lacks the E2 gene region.

Please replace paragraph [0011] with the following amended paragraph that also includes a correction of a publishing error by the PTO:

[0011] The invention additionally provides a cell comprising a recombinant vector, wherein the recombinant vector comprises in operable combination: a) a nucleotide sequence of interest having a 5' end and a 3' end; b) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; c) adenovirus packaging sequence linked to one of the inverted terminal repeats; and d) a first adeno-associated virus terminal repeat sequence operably linked to the 3' end of the nucleotide sequence of interest, wherein the vector lacks a second adeno-associated virus terminal repeat sequence. Without intending to limit the cell to any particular type or source, in one embodiment, the cell is a cell line. In a preferred embodiment, the cell line is selected from a HeLa-derived cell line, A549-derived cell line, 293-derived cell line, HepG2-derived cell line, COS1-derived cell line, HMEC-derived cell line, KB-derived cell line, JW-22-derived cell line, Neo6-derived cell line, and C12-derived cell line. In an alternative embodiment, the cell is a primary cell. In a preferred

embodiment, the primary cell is a human endothelial cell. In another alternative embodiment, the cell is contained in a mammal. In a more preferred embodiment, the mammal is selected from mouse and human. In an alternative embodiment the vector lacks adenovirus E1 gene region, and the cell is capable of expressing adenovirus E1 gene region. In a preferred embodiment, the cell is a 293-derived cell. In another alternative embodiment, the vector lacks adenovirus E1 gene region and further lacks adenovirus E3 gene region. In a preferred embodiment, the cell is a 293-derived cell. In yet another alternative embodiment, the vector lacks adenovirus E3 gene region. In a further alternative embodiment, the vector lacks adenovirus E4 gene region, ~~a nd~~ and the cell is capable of expressing adenovirus E4 gene region. In a preferred embodiment, the cell is a W162-derived cell. In another embodiment, the vector lacks adenovirus E2 early gene region, and the cell is capable of expressing adenovirus E2 early gene region.

Please replace paragraph [0015] with the following amended paragraph:

[0015] The invention additionally provides a first method comprising: a) providing: i) a first recombinant vector as described above [i.e., a recombinant vector, comprising in operable combination: a) a nucleotide sequence of interest having a 5' end and a 3' end; b) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; c) adenovirus packaging sequence linked to one of the inverted terminal repeats; and d) a first adeno-associated virus terminal repeat sequence operably linked to the 3' end of the nucleotide sequence of interest, wherein the vector lacks a second adeno-associated virus terminal repeat sequence], wherein the first vector lacks one or more adenovirus early gene ~~region~~ regions selected from E1, E2, E3, and E4 gene ~~region~~ regions; and ii) a cell capable of expressing the one or more adenovirus early gene ~~which is~~ regions which are lacking from the first vector; b) introducing the first vector into the cell to produce a transformed cell; and c) culturing the transformed cell under conditions such that a second vector is produced, the second vector selected from the recombinant vector described above [i.e., a recombinant vector, comprising in operable combination: a) adeno-associated virus terminal ~~repeat-DD~~ repeat-DD sequence; b) first and second inverted copies of a nucleotide sequence of interest flanking the adeno-associated virus terminal repeat-DD sequence; c) left and right inverted

terminal repeats of adenovirus flanking the first and second inverted copies of the nucleotide sequence of interest; and d) first adenovirus packaging sequence linked to one of the inverted terminal repeats] and a recombinant vector comprising in operable combination: i) a nucleotide sequence of interest having a 5' end and a 3' end; ii) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; and iii) adenovirus packaging sequence linked to one of the inverted terminal repeats. In one embodiment, the recombinant vector further comprises first and second inverted copies of adeno-associated virus terminal ~~repeat-DD~~ repeat-DD sequence flanking the nucleotide sequence of interest, and optionally further comprises a second adenovirus packaging sequence linked to one of the inverted terminal repeats. In another preferred embodiment, invention provides a second method in which the cell is capable of expressing one or more Rep proteins, and the culturing results in expression of the one or more Rep proteins. In yet another preferred embodiment, the second vector is encapsidated. In a more preferred embodiment, the method further comprises d) recovering the encapsidated second vector. In yet a more preferred embodiment, the method further comprises e) purifying the recovered encapsidated second vector. In an alternative more preferred embodiment, the method further comprises e) administering the purified encapsidated second vector to a host cell. In a more preferred embodiment, the administering is under conditions such that the nucleotide sequence of interest in the encapsidated second vector is expressed. In an alternative more preferred embodiment, the host cell is a cultured cell. In another alternative more preferred embodiment, the host cell is comprised in a mammal. In a yet more preferred embodiment, the mammal is selected from mouse and human. In another preferred embodiment, expression of one or more Rep ~~proteins is~~ proteins are inducible.

Please replace paragraph [0016] with the following amended paragraph:

[0016] Also provided herein is a third method, comprising: a) providing: i) a first recombinant vector as described above [i.e., a recombinant vector, comprising in operable combination: a) a nucleotide sequence of interest having a 5' end and a 3' end; b) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; c) adenovirus packaging sequence linked to one of the inverted terminal repeats; and d) a first

adeno-associated virus terminal repeat sequence operably linked to the 3' end of the nucleotide sequence of interest, wherein the vector lacks a second adeno-associated virus terminal repeat sequence], wherein the first vector lacks one or more adenovirus early gene ~~region~~ regions selected from E1, E2, and E4 gene ~~region~~ regions; ii) a cell capable of expressing one or more Rep proteins; and iii) helper adenovirus; b) introducing the first vector and genome of the helper adenovirus into the cell to produce a transformed cell; and c) culturing the transformed cell under conditions such that the transformed cell expresses the one or more Rep proteins, and a second vector is produced, the second vector selected from the recombinant vector described above [i.e., a recombinant vector, comprising in operable combination: a) adeno-associated virus terminal ~~repeat-DD~~ repeat-DD sequence; b) first and second inverted copies of a nucleotide sequence of interest flanking the adeno-associated virus terminal repeat-DD sequence; c) left and right inverted terminal repeats of adenovirus flanking the first and second inverted copies of the nucleotide sequence of interest; and d) first adenovirus packaging sequence linked to one of the inverted terminal repeats] and a recombinant vector comprising in operable combination: i) a nucleotide sequence of interest having a 5' end and a 3' end; ii) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; and iii) adenovirus packaging sequence linked to one of the inverted terminal repeats. In a preferred embodiment, the recombinant vector further comprises first and second inverted copies of adeno-associated virus terminal repeat D sequence flanking the nucleotide sequence of interest, and optionally further comprises a second adenovirus packaging sequence linked to one of the inverted terminal repeats. In a more preferred embodiment, the cell lacks expression of the one or more adenovirus early gene ~~region which is~~ regions which are lacking from the first vector.

Please replace paragraph [0017] with the following amended paragraph:

[0017] The invention provides yet a fourth method, comprising: a) providing: i) a first recombinant vector of as described above [i.e., a recombinant vector, comprising in operable combination: a) a nucleotide sequence of interest having a 5' end and a 3' end; b) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; c) adenovirus packaging sequence linked to one of the inverted terminal repeats; and d) a first

adeno-associated virus terminal repeat sequence operably linked to the 3' end of the nucleotide sequence of interest, wherein the vector lacks a second adeno-associated virus terminal repeat sequence], wherein the first vector lacks one or more adenovirus early gene ~~region~~ regions selected from E1, E2, and E4 gene ~~region~~ regions; ii) a cell capable of expressing the one or more adenovirus early gene ~~which is~~ regions which are lacking from the first vector; and iii) adeno-associated virus; b) introducing the first vector and genome of the adeno-associated virus into the cell to produce a transformed cell; and c) culturing the transformed cell under conditions such that a second vector is produced, the second vector selected from the recombinant vector described *supra* [i.e., a recombinant vector, comprising in operable combination: a) adeno-associated virus terminal ~~repeat DD~~ repeat-DD sequence; b) first and second inverted copies of a nucleotide sequence of interest flanking the adeno-associated virus terminal repeat-DD sequence; c) left and right inverted terminal repeats of adenovirus flanking the first and second inverted copies of the nucleotide sequence of interest; and d) first adenovirus packaging sequence linked to one of the inverted terminal repeats] and a recombinant vector comprising in operable combination: i) a nucleotide sequence of interest having a 5' end and a 3' end; ii) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; and iii) adenovirus packaging sequence linked to one of the inverted terminal repeats. In one preferred embodiment, the recombinant vector further comprises first and second inverted copies of adeno-associated virus terminal repeat D sequence flanking the nucleotide sequence of interest, and optionally further comprises a second adenovirus packaging sequence linked to one of the inverted terminal repeats.

Please replace paragraph [0019] with the following amended paragraph:

[0019] The invention provides a seventh method comprising: a) providing: i) a first recombinant vector as described above [i.e., a recombinant vector, comprising in operable combination: a) a nucleotide sequence of interest having a 5' end and a 3' end; b) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; c) adenovirus packaging sequence linked to one of the inverted terminal repeats; and d) a first adeno-associated virus terminal repeat sequence operably linked to the 3' end of the

nucleotide sequence of interest, wherein the vector lacks a second adeno-associated virus terminal repeat sequence], wherein the nucleotide sequence of interest in the first vector comprises adeno-associated virus rep gene region; and ii) a cell; b) introducing the first vector into the cell to produce a transformed cell; and c) culturing the transformed cell under conditions such that the transformed cell expresses one or more Rep proteins, and a second vector is produced, the second vector selected from the recombinant vector described above [i.e., a recombinant vector, comprising in operable combination: a) adeno-associated virus terminal ~~repeat-DD~~ repeat-DD sequence; b) first and second inverted copies of a nucleotide sequence of interest flanking the adeno-associated virus terminal repeat-DD sequence; c) left and right inverted terminal repeats of adenovirus flanking the first and second inverted copies of the nucleotide sequence of interest; and d) first adenovirus packaging sequence linked to one of the inverted terminal repeats] and a recombinant vector comprising in operable combination: i) a nucleotide sequence of interest having a 5' end and a 3' end; ii) left and right inverted terminal repeats of adenovirus flanking the nucleotide sequence of interest; and iii) adenovirus packaging sequence linked to one of the inverted terminal repeats. In one preferred embodiment, the recombinant vector further comprises first and second inverted copies of adeno-associated virus terminal repeat D sequence flanking the nucleotide sequence of interest, and optionally further comprises a second adenovirus packaging sequence linked to one of the inverted terminal repeats. In a more preferred embodiment, the first vector lacks one or more adenovirus early gene ~~region~~ regions selected from E1, E2, and E4 gene ~~region~~ regions, and the cell is capable of expressing the adenovirus early gene region which is lacking from the first vector. In an alternative more preferred embodiment, the first vector lacks adenovirus E3 gene region.

Please replace paragraph [0035] with the following amended paragraph:

[0035] The terms "lack" and "lacking" a nucleotide sequence when made in reference to a vector means that the vector contains at least one deletion (*i.e.*, absence of one or more nucleotides) in the nucleotide sequence. Deletions may be continuous (*i.e.*, uninterrupted) or discontinuous (*i.e.*, interrupted). Deletions may lie in a coding sequence or a regulatory sequence. A ~~deletions~~ deletion can be a partial deletion (*i.e.*, involving removal of a portion

ranging in size from one (1) nucleotide residue to the entire nucleic acid sequence minus one nucleic acid residue) or a total deletion of the nucleotide sequence. Deletions are preferred which prevent the production of at least one expression product encoded by the nucleotide sequence. For example, a vector which lacks ~~adenovirus~~ an adenovirus E1 gene region refers to a vector which contains at least one deletion in the E1 gene region. Preferably, though not necessarily, the deletion prevents the production of at least one of the multiple proteins encoded by the E1 gene region.